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How Wounding via Lasers Has Potential Photocarcinogenic Preventative Effects via Dermal Remodeling

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Abstract

As the incidence of non-melanoma skin cancer (NMSC) is increasing, there is a growing need to identify effective preventive strategies. A recently proposed hypothesis states that NMSC photocarcinogenesis is tightly linked to insufficient insulin growth factor-1 expression by agglomerated senescent fibroblasts in geriatric dermis. This paucity of IGF-1 expression in senile skin allows basal keratinocytes to mitotically propagate their UVB-altered genome and potentially initiate an actinic neoplasm. Here we review the role of the dermal microenvironment in NMSC pathogenesis, describe the impact of fibroblast senescence on this process and discuss how laser-induced dermal wounding can be effectively used to prevent NMSC development in geriatric patients.

Keywords

UVB; non-melanoma skin cancer (NMSC); squamous cell cancer (SCC); insulin growth factor-1 receptor (IGF-1R); fibroblast senescence; fractionated laser resurfacing (FLR)

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest

Dr. Aleksandar Krbanjevic, Dr. Jeffrey B. Travers, and Dr. Dan F Spandau declare that they have no conflicts of interest.

INTRODUCTION

Cancers of the skin are the most common of all types of cancers according to the American Cancer Society (1), existing predominantly as basal cell carcinoma, squamous cell cancer (SCC) and melanoma. The first two which can be grouped as non-melanoma skin cancers (NMSC), occur in more than 2.2 million patients in the United States each year (1,2). The enormity of NMSC incidence necessitates more intensive translational cutaneous research that will develop preventive as well as therapeutic strategies in dermato-oncology. In this review, we will illustrate how results of a "bench-to-bedside" strategy in modern medicine can propose an expansion of common uses of therapeutic lasers in preventive dermatology. We are thus hoping to offer a basic science justification why an ounce of potential prophylactic treatment for SCC is worth a pound of its cure (3).

Notably, many signaling pathways have been investigated thus far in the context of how epidermal keratinocytes upon life-time exposure to UVB, eventually accumulate radiation-induced DNA damage (4,5). Nevertheless, none of these pathways was able to offer a good justification of evident epidemiological data - why NMSC primarily occurs in the elderly. It is logical to target basic science efforts to examine signaling pathways frequently disturbed in geriatric skin following UVB irradiation. The insulin-like growth factor-1/insulin-like growth factor-1 receptor (IGF-1/IGF-1R) pathway (6–8) is one such pathway. Recent published reports have shown that the severity of DNA damage in keratinocytes directly correlates to the intensity of UVB exposure and that the state of activation of the IGF-1/IGF-1R pathway is critical to propensity of one to develop the NMSC. Furthermore, this activation is directly linked to the cellular senescence profile of dermal fibroblasts in the dermal-epidermal niche in aged skin. More precisely, the production of IGF-1 found in dermal fibroblasts of young skin is suppressed in older, geriatric skin. This loss of IGF-1 expression in geriatric skin has severe consequences on how geriatric keratinocytes react to UVB exposure. Keratinocytes could have several destinies depending on the dose of UVB light and the pre-existing activity of IGF-1/IGF-1R pathway. This behavior is mostly observed in response to intermediate doses of UVB: (a) if the IGF-1R is active, keratinocytes partially repair their DNA and favorably undergo stress-induced senescence, but (b) if the IGF-1R is inactive, keratinocytes cannot repair DNA damage and either continue to proliferate carrying malignancy prone DNA damage or under rare occasions are predetermined toward apoptosis (8–11).

Clinical value of these fundamental findings is immense. They led to evolution of new translational therapeutic approaches in geriatric patients predisposed and exposed to SCC (12). The idea of overturning the fibroblast senescence phenotype by wounding modalities is now appealing clinically and will be further discussed in this review.

Risk factors for squamous cell carcinoma

NMSC, like other neoplastic pathologies, is characterized by multifactorial origin. Though the precise causal mechanism has not being defined, epidemiological studies suggest an interplay of genetic, environmental and advancing aging causalities. NMSC is more prevalent in males, patients who have light-colored skin and blue eyes, are immunosuppressed (primary or secondary), infected by human papilloma viruses (HPV) or

exhibit some chronic inflammatory states (scars, burns or sinus tracts). In addition, several genetically inherited cutaneous conditions could also carry high risk for NMSC, for instance xeroderma pigmentosum, oculocutaneous albinism and epidermodysplasia verruciformis (13,14).

However, the most likely direct causes of NMSC are sunlight and advancing age (5,15–17). This epidemiological link was well-established clinically, as more than 80% of NMSC patients are older than 60 and their lifestyle is connected to prolonged sunlight exposure (18). Nevertheless, this clinical observation has not offered a direct causal link between the three associated phenomena: the cancer, sun exposure and older age, instead–it geared basic science research toward linking UV radiation of sunlight and molecular mechanisms of carcinogenesis in elderly. Initial reports suggest that excessive sun exposure in juvenescence can cause accumulation of UBV-induced mutations in epidermal keratinocytes (19). These DNA alterations are not sufficient to cause the keratinocytes death but rather allow them to silently persist in epidermis for decades where they will progressively accumulate novel and certainly deleterious mutations. When the number of these DNA mutations in essential regulatory genes reaches still not defined threshold, abnormal keratinocyte divisions will ensue, initiating the tumor growth and making the cancer clinically apparent (20). However, this traditional approach of accumulation of chromosomal impairments has being non-selectively applied to many neoplastic processes in oncology. In skin cancer pathogenesis, it relies on very weak mathematical premises that sun exposure in youth is higher than in adulthood and that skin defense strategy against malignancy remains unaltered throughout lifetime (18). Recently however, several groups have proved that neither was the case–as almost 80% of our exposure to sunlight occurs after puberty and this exposure remains constant throughout our lifetime (18,21). The UVB component in sunlight induces distinct types of DNA damage in keratinocytes, i.e. DNA single strand breaks, DNA interstrand cross-links, as well as nucleotide base modifications. Such DNA damages threaten genomic stability of keratinocytes forcing them to acquire adaptive behavior to effectively repair their DNA, successfully undergoing programmed cell death and/or purposely undergoing premature senescence so as to evade neoplastic transformation. Along these lines, several groups have shown the ability of aging skin to repair UV-induced oxidative DNA damage diminishes over time (22,23). This photoaging process is primarily due to loss of nuclear DNA base excision repair enzymes, as well as, DNA nucleotide excision repair enzymes (24).

Much research on the pathogenesis of photoaging has also implicated important roles for cytokines and growth factors (regeneration of epidermis), diminished melanogenesis (decreased melanin protection), and inefficient fibroblast deposition of collagenases and elastases (failure to remove misfolded collagen and elastin) (24). All of these basic science reports enlighten the complexity of NMSC pathogenesis further suggesting that NMSC is a gradually life-evolving sun induced process and as such partially manageable by actinic radiation protective therapy (25–27).

In the last decade, the IGF-1/IGF-1R signal transduction pathway has attracted much attention in the basic research community suggesting this pathway as a novel mechanism that might explain why NMSC is a disease of the elderly (7–11). Not only that this

mechanism highly correlates with clinical observations but it considerably enlightens the disease development in geriatric population. Additionally, its value stands in proposing possible preventive strategies that could target premalignant lesions like actinic keratosis (AK) and hopefully forestall their progress into clinically manifested disease in receptive patients.

Molecular basis of squamous cell carcinoma pathogenesis in elderly–a new concept

A key limitation of NMSC basic research was inability to sufficiently correlate obtained data with clinical and epidemiological studies - primarily how lifetime exposure to UV radiation leads to development of actinic malignancy in the senior population (5). To our knowledge, UVB-induced stromal changes in aging skin have scarcely been investigated as a contributing factor in pathogenesis of these neoplasms. Recently, new light has been shown on this phenomenon by proposing a paradigm that not only suggests direct causality between the two, but also offers the cancer preventive treatments based on skin rejuvenation procedures already available in many dermatological practices.

When UVB-photons hit the epidermis, they first damage keratinocyte nucleic acids causing their signature mutations. If these mutations are not repaired but rather preserved and carried on to subsequent keratinocytes' offspring, these cells have a propensity to eventually undergo neoplastic transformation (28). This keratinocyte procarcinogenic fate is not as easy to achieve as they have developed constitutional mechanisms to fight UVB-induced DNA damage (29). Our basic research findings revealed that the IGF-1/IGF-1R signaling pathway in human skin is one of these protective mechanisms. This pathway is compartmentalized within the dermal-epidermal junction where dermal fibroblasts (for now unilaterally) regulate the keratinocyte differentiation destiny. The basic components of this signaling mechanism are a tyrosine kinase family member, the IGF-1R (30) expressed on keratinocytes and the IGF-1R binding ligand, IGF-1, secreted extracellularly by dermal fibroblasts.

While the IGF-1R is expressed on human epidermal keratinocytes, IGF-1 mRNA/protein is detected in dermal fibroblasts, and melanocytes, but not in keratinocytes (30). Hence, the predominant mechanism by which the keratinocyte's IGF-1R can be activated is by IGF-1 secreted by papillary dermal fibroblasts. This signaling synergistic mechanism is maintained throughout lifetime allowing normal survival and growth of healthy skin. The aging process significantly affects fibroblast's ability to synthesize and secrete IGF-1 in vivo. Consequently, the paucity of IGF-1 ligand in aged dermis significantly diminishes IGF-1R activation on keratinocytes. This receptor activation is crucial for keratinocytes to effectively respond to UVB irradiation in aged skin. In young skin, IGF-1 synthesis and secretion are sufficient to maintain normal activity of the keratinocyte IGF-1R. When exposed to moderate levels of UVB, DNA of young keratinocytes undergoes radiation-induced damage. This damage, if it cannot be fully repaired, predestines keratinocytes to become senescent. Keratinocyte senescence is a tumor evasion mechanism which averts these cells from passing actinic-induced mutations to their daughter cells. Unfortunately, the geriatric keratinocytes due to inactivity of protective IGF-1R signaling are not able to induce senescent response under the same dose of UVB. This biological misfortune causes them to

propagate UVB-induced DNA damage and ultimately induce neoplastic transformation in keratinocytes (6,8).

The importance of the IGF-1/IGF-1R pathway comes into play when UVB irradiation is within intermediate intensity levels. If this pathway is active, this intermediated level of radiation causes intermediate levels of DNA damage. If this damage cannot be completely repaired, keratinocytes will undergo stress-induced senescence (6). This mechanism thus clears these cells from entering the cell cycle and propagating damage to subsequent generations. In addition, this mechanism still preserves these cells in epidermis therefore preventing the skin from losing its barrier function. By contrast, if IGF-1/IGF-1R pathway is inactive as is the case during sun exposure in the elderly, the keratinocytes with intermediately mutated DNA not only cannot repair their genome, but also will keep proliferating dispersing therefore further their neoplastic potential. However, high and low UVB doses appear not to depend on activity of the IGF-1/IGF-1R pathway. Keratinocytes with slightly damaged DNA are able to completely repair their genome and survive independently of the IGF-1R activity. Similarly, cells with substantially damaged DNA cannot be rescued by preserved IGF-1R activity and are entirely removed from skin by apoptosis (20).

Encouraged by this basic science work, we examined further applicability of the IGF-1R activation in clinics in order to understand increased susceptibility of geriatric patients to NMSC. We observed that skin of patients older than 65 contained more senescent dermal fibroblasts than skin of patients younger than 25. This increase correlated with decrease in IGF-1 expression and consequent epidermal IGF-1R activation. We found that IGF-1R activation is crucial for keratinocyte response to UVB irradiation as in its absence, UVB damaged basal keratinocytes are able to proliferate and propagate their sun-exposed DNA damage. Notably, by injecting recombinant IGF-1 into the dermis of geriatric patients we were able to restore healthy skin response to UVB irradiation demonstrating a reversible nature of this important signaling pathway, as well as opening new avenues for promising therapeutic interventions (6–8).

Prophylactic wounding therapies – a theory behind praxis

NMSC with its annual incidence of over 2 million cases still represents the most common cancer in the United States (1). Such a high incidence of these malignancies presents a significant clinical and economic burden to the United States healthcare system and urges a public demand for its control. Prevention of tumors before they become clinically manifested has always been the most affordable though not necessarily the most elusive way. SCC is considered to evolve from pre-cancerous entity - the actinic keratosis (AK) (31), a lesion previously been shown to be somewhat manageable by cryotherapy, curettage, electrosurgery and photodynamic therapy with 5-fluorouracil or topical imiquimod (32,33). It has been shown that if treat AK by these modalities early enough that the progression to SCC is highly unlikely. Still some patients do develop SCC recurrences within 2–5 year period advocating prolonged clinical surveillance of pre-cancerous lesions and consequently increasing financial cost to our healthcare system (20,34).

Even though the efficiency of AK treatment modalities in clinics has been improved in recent years, the major progress has been primarily achieved by minimizing evolution of already existing AK or early grade SCC lesions. Additionally, these treatment modalities target only clinically confirmed lesions and miss histologically appearing silent skin which could harbor pre-malignant lesions. This unaffected skin in aged individuals will remain fertile ground for development of actinic pre- or neoplastic processes if left prophylactically untreated and further exposed to sun radiation. Therefore, in the light of recent basic science findings that aged skin is specifically susceptible to UVB, it is possible to further improve skin rejuvenation modalities by combining them with the dermal IGF-1 restoration strategies. With this goal in mind, these skin rejuvenation strategies will acquire a new role in modern dermatological practices that not only have cosmetic but also cancer prophylactic effects (34–38). Our group has already shown that dermabrasion and fractionated laser resurfacing are promising rejuvenation strategies that can fulfill these roles in modern dermatology (12). At this point it is still not known molecularly how these cosmetic modalities rejuvenate the skin and prevent its neoplastic transformation–they could just physically remove senescent fibroblast causing the “wounded” skin to repopulate itself with new cells or by activating migration cues of fibroblasts into the treated tissues or “simply” by affecting the cell signaling mechanisms that regulate gene expression, protein translation or stimulate protein secretion of IGF-1, collagen and elastin. Further translational research is therefore required to elucidate these beneficial molecular mechanisms before we can use their results successfully in clinical settings.

Remodeling therapies reverse aging-induced senescence

The recent advent of basic science data that highlight importance of dermal fibroblast senescence as a contributing, if not predominant, factor in geriatric skin propensity to develop UVB-induced neoplasms led us to test molecular signaling behind clinically successful skin resurfacing modalities that are shown to reinstate youthful signaling in geriatric patients (12,39). Our group has examined molecular mechanisms that underlie two clinically successful skin wounding modalities, a dermabrasion and fractionated laser resurfacing methods. Dermabrasion is a 40-year known wounding modality featured by superficial dermal lesioning by rough grain sandpaper. Initial research has documented that the production of new collagen fibrils underlies this wounding modality. We were curious to investigate molecular and cellular changes in volunteers undergoing this treatment. In order to analyze the skin of geriatric individuals (age > 65 years), we first dermabraded distinct areas of their skin; three months later, the dermabraded loci were exposed to medium doses of UVB and subsequently the punch-out biopsies were taken for histological and biochemical analyses. Our group was the first to show that dermabrasion produced skin scarce in senescent fibroblasts but with fully restored levels of dermal IGF-1 mRNA. In addition, histologically we observed accumulation of elliptical fibroblast-replicating nuclei, denser fibroblast distribution, restoration of collagen fiber layers in the dermis, recovery of undulating dermal-epidermal basal membrane, and increased number of replicative keratinocytes - all featured in younger skin. Importantly, the levels of restored IGF-1 were quite comparable to those detected in skin from young individuals (age < 30 years). Furthermore, we were not able to detect significant population of initiated (UVB-damaged) basal keratinocytes in dermabrasion-treated epidermis suggesting that the potential for

progression of these foci into SCC was drastically diminished (11). This work was pioneering since no-one before has shown reversible molecular signature induced by dermabrasion that could overcome favorably senile pro-carcinogenic UVB response. Interestingly, many epidemiological studies have documented that dermabrasion reduces the incidence of AK and SCC by 95% many years after the application. Still significant morbidity that remains after this procedure renders dermabrasion less favorable in a routine clinical praxis.

Although a powerful strategy, the significant cosmetically unacceptable outcomes associated with dermabrasion lead us to investigate whether another potent but less aggressive rejuvenation treatment, the fractionated laser resurfacing (FLR; using a 2790nm vittrium scandium gallium garnet ablative fractional resurfacing device; Pearl Fractional Laser, Cutera, Brisbane CA), is able to alleviate the inept UVB response of geriatric skin. In FLR a pulsating laser beam delivers high-energy to skin chromophores and tissue water. The energy of laser photon in interaction with skin surface diffracts and part of its energy releases as a heat. The energy of heat causes skin vaporization of tissue layers inducing formation of mini-wounds. These mini-wounds induce a discrete “wounding reactions” (discrete microscopic columns of ablated epidermis and dermis in regularly spaced arrays) and damage that is eventually repopulated by new skin cells (12). The clinical consequence of this treatment modality is increased superficial skin tension still more favorable than profound massive superficial lesions commonly observed after dermabrasion. Although the dermatological lasers have commonly being used in practice for almost two decades, their histological and molecular mechanism of actions on skin, especially in restoring inadequate UVB response in elderly, has not being fully elucidated. In order to thoroughly explore their mode of action, we examined the skin in elderly volunteers. We found that independently of tissue sun exposure, FLR reduced the proportion of senescent fibroblasts, increased the production of dermal IGF-1, and normalized the skin response to UVB in treated foci (Fig. 1, 12). Notably, these effects were also observed in more aggressive dermabrasion procedure. More importantly, our basic science work offers an extension of clinical indications of FLR now to prophylaxis of future SCC. Extraordinarily, it appears that FLR provides extended protection of actinic-induced neoplasms for up to two years longer than commonly used sun protection methods in elderly. Although promising as a preventive strategy for skin cancer, ablative lasers in cosmetology are associated with various side effects mild (and common) like redness, itching, acne and skin discoloration but also with serious (and rare) like skin infection, blistering and permanent scarring. Apparently, more translation research is necessary to make this rejuvenation modality as comfortable as successful it is.

CONCLUSIONS

The novel work of several translational groups including ours has elucidated some mechanisms of skin resurfacing methodologies and proposes an extension of laser indications in clinical dermatology. Our effort to understand the nature of lasers and the biology of senescent fibroblasts in aged skin is ongoing. This new concept of restoring youth of skin by lasers will hopefully allow dermatologist to precisely dose the frequency, amplitude and timing of clinical lasers in order to diminish their side effects and offer as best

service as possible to their ever increasing elderly population. Moreover, the old adage "*fight fire with fire*" finds its full application in modern dermatology where a light-induced disease appears to be best treated with a light-preventive strategy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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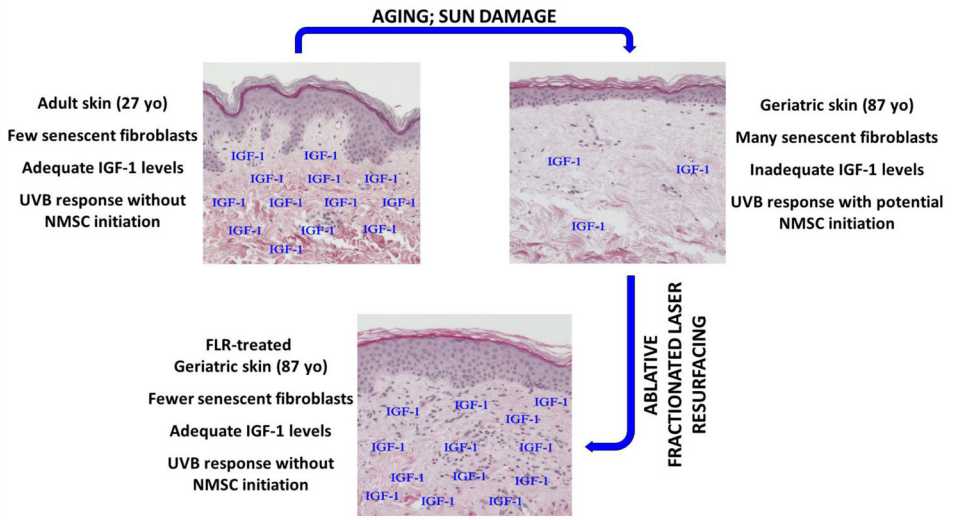

Figure 1. Model demonstrating influence of Fractionated Laser Resurfacing on the response of geriatric skin to UVB irradiation

The top two panels compare features of young adult skin (left panel) and geriatric skin (right panel). Notice atrophy of epidermis and flattening of basement membrane in the geriatric skin. The increased proportion of senescent fibroblasts in the geriatric skin, and corresponding decrease in IGF-1 expression, leads to an enhanced susceptibility to development of UVB-induced NMSC. Following FLR treatment of geriatric skin (lower panel), the thickness of epidermis is increased and there is a restoration of undulating nature of the epidermal/dermal junction. In addition, the proportion of senescent fibroblasts is reduced, the level of IGF-1 expression increased, and there is a decreased susceptibility to UVB-induced NMSC.